

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020916

MICROBIOLOGY REVIEW(S)

JUL 24 1998

MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS
(HFD-590)

NDA# 20-916

REVIEWER: Linda J. Utrup, Ph.D.

CORRESPONDENCE DATE: Sept. 30, 1997

CDER RECEIPT DATE: Oct. 1, 1997

REVIEW ASSIGN DATE: Oct. 10, 1997

REVIEW COMPLETE DATE: June 15, 1998

SPONSOR: Astra Merck
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Phone # 610-695-1008
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Contact: Gary Horowitz, Ph.D.

SUBMISSIONS REVIEWED: Original NDA

DRUG CATEGORY: Anti *Helicobacter pylori*

INDICATION: Omeprazole in combination with clarithromycin plus amoxicillin for eradication of *H. pylori* and reduction of the risk of duodenal ulcer recurrence.

DOSAGE FORM: Omeprazole - capsules, oral 20 mg

PRODUCT NAMES:

- a. PROPRIETARY: Prilosec Delayed-Release Capsules
- b. NONPROPRIETARY: Omeprazole
- c. CHEMICAL: 5-methoxy-2-[[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole

STRUCTURAL FORMULA:

MW = 345.42

SUPPORTING DOCUMENTS: IND IND

BACKGROUND:

Data were submitted from three US randomized, double-blind clinical trials to evaluate the safety and efficacy of omeprazole given in combination with amoxicillin and clarithromycin (O+A+C) for 10 days. The indication sought is treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or up to 5- year history) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

Two clinical trials were conducted by Astra Merck (126 and 127) and one (M96-446). The triple therapy regimen (O+A+C) was compared to amoxicillin plus clarithromycin (A+C) with an omeprazole placebo. Studies 126 and 127 were conducted in patients with an active duodenal ulcer and the other study (M96-446) was conducted in patients with a history of a duodenal ulcer in the past 5 years but without an ulcer present at the time of enrollment. There were a total of 558 patients in the three studies.

The dose regimen used in the three studies was omeprazole 20 mg bid plus clarithromycin 500 mg bid plus amoxicillin 1 g bid for 10 days; or clarithromycin 500 mg bid plus amoxicillin 1 g bid for 10 days. In studies 126 and 127, patients who took the omeprazole regimen also received an additional 18 days of omeprazole 20 mg qd. Endpoints studied were eradication of *H. pylori* (all studies) and duodenal ulcer healing (studies 126 and 127 only). *H. pylori* status was determined by CLOtest, histology and culture in all three studies. The determination of success or failure for a given patient was done according to the FDA evaluability criteria. Patients from all three studies were to have a culture taken pretreatment and post-treatment. Susceptibility testing was to be performed whenever the culture was positive according to the protocols.

SUMMARY:

For the culture and susceptibility testing analysis, one antral and one corporeal biopsy specimen was obtained from each patient at baseline and at 4 to 6 weeks post-treatment.

Ampicillin (used to estimate susceptibility to amoxicillin), metronidazole and clarithromycin susceptibility testing by the Etest methodology was performed when *H. pylori* was present. Since Etest MICs values are 1/2 the typical doubling dilutions the next higher MIC was considered comparable to the agar dilution MIC and was used in the analysis.

All available isolates were initially tested using the Etest methodology. Because agar dilution has now been recognized by the NCCLS as the methodology of choice for *H. pylori*, the sponsor agreed to retest a subset of isolates using the current NCCLS approved agar dilution methodology. The isolates tested were selected according to the following criteria: all pre- and post-treatment pairs, all post-treatment isolates, pretreatment isolates with MIC values (by Etest) ≥ 0.06 mcg/mL for clarithromycin and any isolates with an ampicillin MIC value (by Etest) ≥ 0.25 mcg/mL. In addition, only one isolate (antral or corporeal) was tested per endoscopy for both antibiotics, and the specimen with the highest MIC value by Etest was chosen. In the case that the two antibiotics presented the highest MIC values on different specimens from the same endoscopy, the antral and corporeal specimens were both tested for susceptibility to amoxicillin and clarithromycin. Since most of the isolates used for agar dilution testing were selected because they were pre-treatment and post-treatment pairs (i.e. *H. pylori* was not eradicated), the subset results would be expected to be biased against successful *H. pylori* eradication.

Microbiology Reviewer's Comment: There were some biopsy specimens for which pretreatment or post-treatment culture and susceptibility results were not available.

The sponsor's interpretive criteria based on the Etest methodology are shown in Table 1.

Table 1. Sponsor's Minimum Inhibitory Concentration (MIC) Interpretive Criteria Based on the Etest Methodology

	Amoxicillin	Clarithromycin
Resistant	> 8 mcg/mL	> 2 mcg/mL
Intermediate	$0.38 < \text{MIC} \leq 8$ mcg/mL	$0.125 < \text{MIC} \leq 2$ mcg/mL
Susceptible	≤ 0.38 mcg/mL	≤ 0.125 mcg/mL

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The sponsor's interpretive criteria based on the agar dilution methodology are shown in Table 2.

Table 2. Sponsor's Minimum Inhibitory Concentration (MIC) Interpretive Criteria Based on the Agar Dilution Methodology

	Amoxicillin	Clarithromycin	
Resistant		> 2 mcg/mL	
Intermediate	-	0.25 < MIC ≤ 2 mcg/mL	APPEARS THIS WAY ON ORIGINAL
Susceptible	≤ 1.0 mcg/mL	≤ 0.25 mcg/mL	

Microbiology Reviewer's comments: Currently, there are no NCCLS interpretive criteria for any antimicrobial agent against H. pylori using any susceptibility testing methodology. Additionally, agar dilution is the reference testing method of choice (not Etest) according to the Helicobacter pylori Susceptibility Testing Standardization Study Group of the NCCLS, as well as FDA. The Study Group also recommends testing with amoxicillin rather than ampicillin.

The Microbiology Reviewer's interpretive criteria are listed in Table 3.

Table 3. FDA Minimum Inhibitory Concentration (MIC) Interpretive Criteria

	Amoxicillin	Clarithromycin	
Resistant		≥ 2 mcg/mL	APPEARS THIS WAY ON ORIGINAL
Intermediate			
Susceptible	≤ 0.25 mcg/mL	≤ 0.25 mcg/mL	

PRETREATMENT MICs

Pretreatment Amoxicillin MIC Results for All Patients in All Three Studies

There were 3/439 patients with pretreatment amoxicillin Etest MICs > 0.25 mcg/mL, the remainder had pretreatment amoxicillin Etest MICs ≤ 0.25 mcg/mL.

When tested by the agar dilution methodology, 2/165 patients had pretreatment MICs > 0.25 mcg/mL and the remaining 163 had agar dilution MICs of ≤ 0.25 mcg/mL.

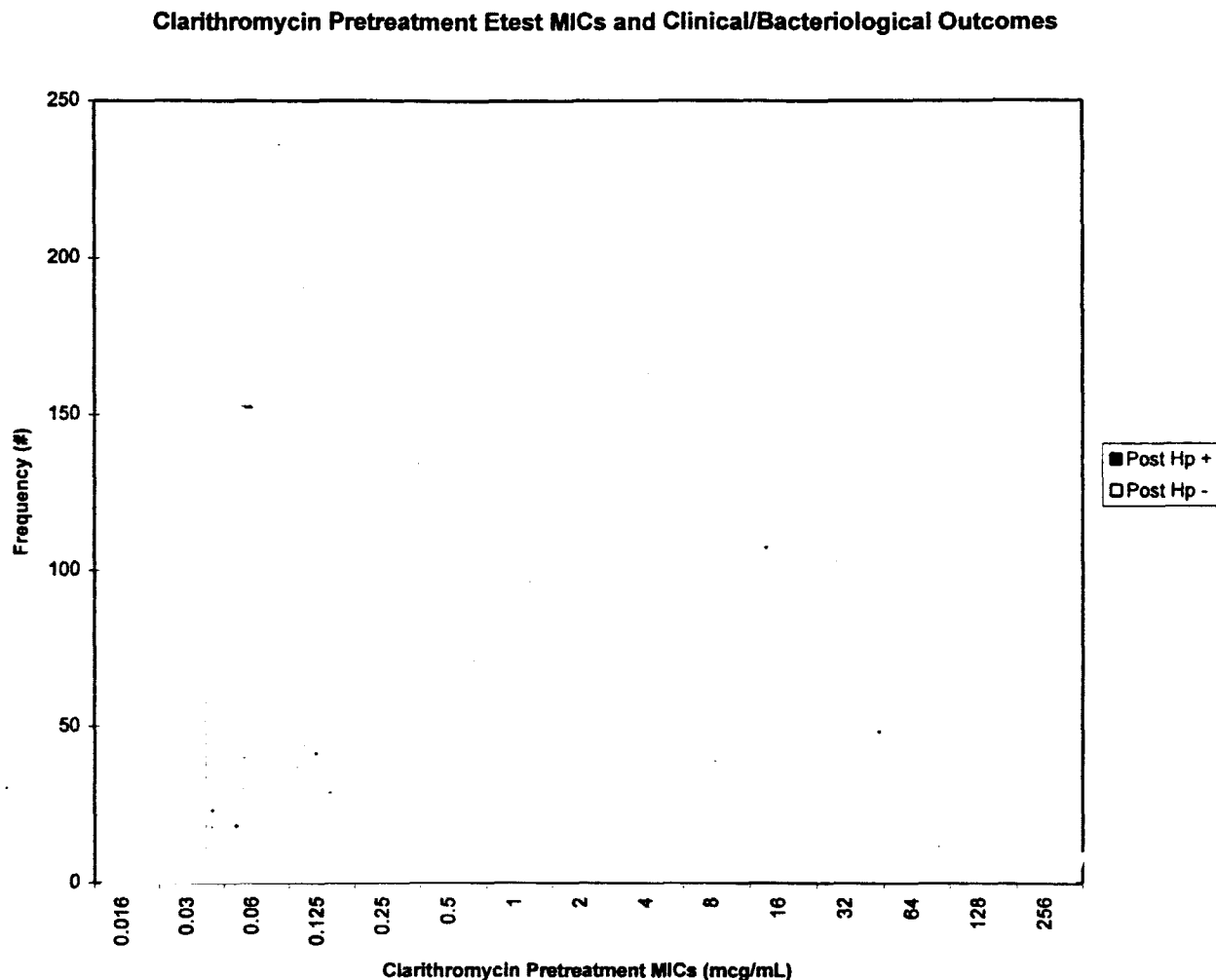
Pretreatment Clarithromycin MIC Results for All Patients in All Three Studies

When using the Etest methodology, 9.3% (41/439) of the patients had clarithromycin resistant pretreatment MICs (≥ 2.0 mcg/mL); 90.2% (396/439) of the patients had clarithromycin susceptible pretreatment MICs (≤ 0.25 mcg/mL); and 0.5% (2/439) of the patients had clarithromycin intermediate pretreatment Etest MICs

The distribution of clarithromycin pretreatment MICs is shown in Fig. 1.

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Fig. 1



One patient each had clarithromycin pretreatment MICs of 0.25, 0.5, and 1.0 mcg/mL who failed therapy and the *H. pylori* was not eradicated. There were 2 patients with MICs of 8 mcg/mL (both failed), 3 with MICs of 16 mcg/mL (1 failed), 2 with MICs of 32 mcg/mL (both failed), 4 patients with MICs of 64 mcg/mL (3 failed) and 1 with an MIC of 128 mcg/mL who failed therapy.

Clinical/Bacteriological Outcomes

Clarithromycin

The clarithromycin agar dilution MIC susceptibility test results and clinical/bacteriological outcomes are listed in Table 4 (Studies 126, 127, M96-446).

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Table 4.

Clarithromycin Susceptibility Test Results (Agar Dilution) and Clinical/Bacteriological Outcomes for All Studies^a

Clarithromycin Pretreatment Results	Clarithromycin Post-treatment Results				
	<i>H. pylori</i> negative - eradicated	<i>H. pylori</i> positive - not eradicated			
		Post-treatment susceptibility results			
		S ^b	I ^b	R ^b	No MIC
Omeprazole 20 mg BID/Clarithromycin 500 mg BID/Amoxicillin 1 g BID for 10 days (126, 127, M96-446)					
Susceptible ^b 24	15	6	2	1	
Intermediate ^b					
Resistant ^b 12	3	6	3		
Clarithromycin 500 mg BID/Amoxicillin 1 g BID for 10 days (126, 127, M96-446)					
Susceptible ^b 95	7	53	9	26	
Intermediate ^b 3		1	1	1	
Resistant ^b 25	2	20	3		

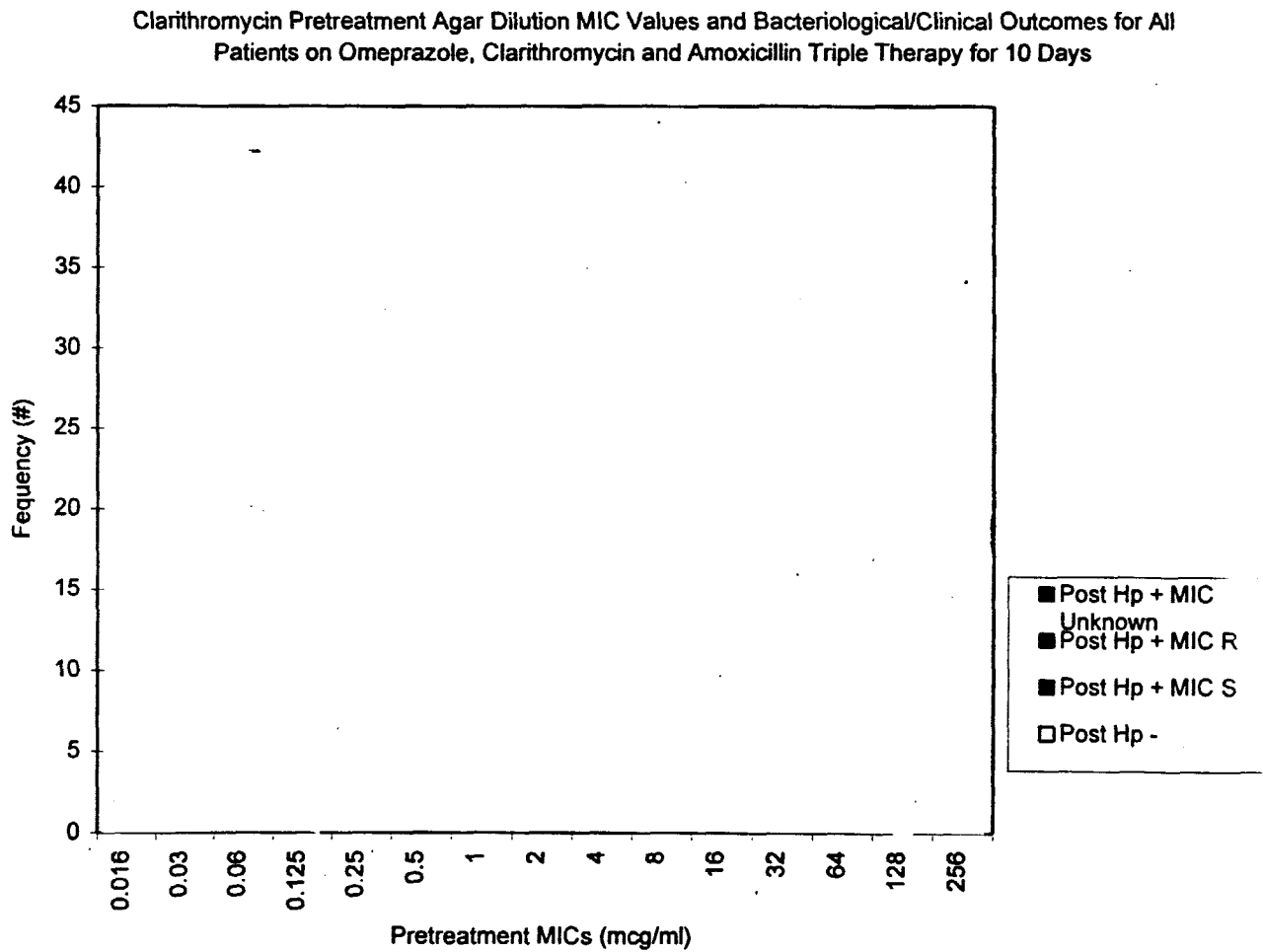
^a Includes only patients with pretreatment clarithromycin susceptibility test results

^b Susceptible (S) MIC ≤ 0.25 µg/mL, Intermediate (I) MIC 0.5 - 1.0 µg/mL, Resistant (R) MIC ≥ 2 µg/mL

The distribution of agar dilution MICs for 36 isolates in the omeprazole, clarithromycin and amoxicillin triple therapy regimen are shown in Figure 2. (The clinical/bacteriological successes are shown in white, while the failures are shown in various shades of gray or black.)

Figure 2.

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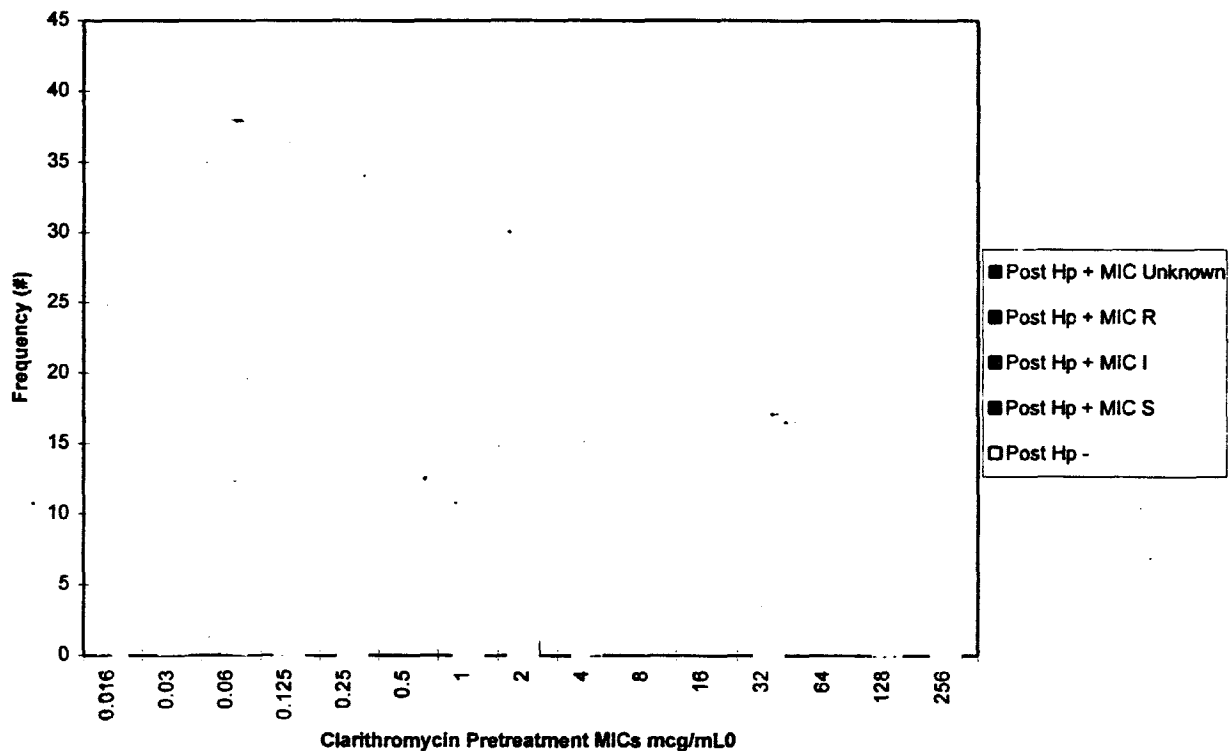
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The distribution of agar dilution MICs for the 123 isolates in the clarithromycin and amoxicillin treatment regimen are shown in Figure 3. (The clinical/bacteriological successes are shown in white, while the failures are shown in various shades of gray or black.)

Figure 3.

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Clarithromycin Pretreatment Agar Dilution MICs and Bacteriological/Clinical Outcomes for Patients on Clarithromycin and Amoxicillin Therapy for 10 Days



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Microbiology Reviewer's Comment: The above charts demonstrate by population distribution and clinical outcome, that the clarithromycin interpretive criteria selected by the FDA are appropriate.

As stated previously the agar dilution MICs were performed on a subset of the population. The total population was tested via the Etest methodology. The clarithromycin MICs obtained by Etest and clinical/bacteriological outcomes are listed in Table 5.

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Table 5.

Clarithromycin Susceptibility Test Results (Etest) and Clinical/Bacteriological Outcomes for All Patients in All Studies^a

Clarithromycin Pretreatment Results	Clarithromycin Post-treatment Results				
	<i>H. pylori</i> negative - eradicated	<i>H. pylori</i> positive - not eradicated			
		Post-treatment susceptibility results			
		S ^b	I ^b	R ^b	No MIC
Omeprazole 20 mg BID/Clarithromycin 500 mg BID/Amoxicillin 1 g BID for 10 days (126, 127, M96-446)					
Susceptible ^b 171	153	7		3	8
Intermediate ^b					
Resistant ^b 14	4	1		6	3
Clarithromycin 500 mg BID/Amoxicillin 1 g BID for 10 days (126, 127, M96-446)					
Susceptible ^b 185	73	73	8	10	21
Intermediate ^b 2				2	
Resistant ^b 24	2			21	1

^a Includes only patients with pretreatment clarithromycin susceptibility test results

^b Susceptible (S) MIC ≤ 0.25 µg/mL, Intermediate (I) MIC 0.5 - 1.0 µg/mL, Resistant (R) MIC ≥ 2 µg/mL

Microbiology Reviewer's Comments:

Emerging Clarithromycin Resistance

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Triple therapy (O+A+C)

Of all the patients with clarithromycin susceptible pretreatment isolates, the overall emerging clarithromycin resistance rate was 1.8 % (3/163) (only patients with post-treatment MICs) or 6.4% (11/171) (considering patients who failed but had no post-treatment MICs to be resistant). Of the patients who failed triple therapy, the emerging resistance rate was 30 % (3/10) (only

patients with post-treatment MICs) or 61.1 % (11/18) (considering patients who failed but had no post-treatment MICs to be resistant).

Dual antimicrobial therapy (A+C)

Of all the patients with clarithromycin susceptible pretreatment isolates, the overall emerging clarithromycin resistance rate was 6.1 % (10/164) (only patients with post-treatment MICs) or 16.8 % (31/185) (considering patients who failed but had no post-treatment MICs to be resistant). Of the patients who failed triple therapy, the emerging resistance rate was 11 % (10/91) (only patients with post-treatment MICs) or 27.7 % (31/112) (considering patients without post-treatment MICs to be resistant).

If the clarithromycin intermediate MICs are considered to be resistant the overall emerging resistance rate was 11 % (18/164) (only patients with post-treatment MICs) or 21.1 % (39/185) (considering patients who failed and did not have post-treatment MICs to be resistant). Of the patients who failed triple therapy, the emerging resistance rate was 19.8 % (18/91) (only patients with post-treatment MICs) or 34.8 % (39/112) (including patients without post-treatment MICs).

Dual therapy (O+C)

Of all the patients with clarithromycin susceptible pretreatment isolates, the overall emerging clarithromycin resistance rate was 26.3 % (26/99) (only patients with post-treatment MICs) or 32.4 % (35/108) (considering patients who failed but had no post-treatment MICs to be resistant). Of the patients who failed triple therapy, the emerging resistance rate was 96.3 % (26/27) (only patients with post-treatment MICs) or 97.2 % (35/36) (worst case-considering patients without post-treatment MICs to be resistant).

The data suggest that adding amoxicillin to the clarithromycin plus omeprazole regimen results in better eradication rates and less emergence of clarithromycin resistance.

Overcoming Pretreatment Resistance

Triple therapy (O+A+C)

Of the 14 patients with pretreatment isolates with clarithromycin resistance, 4 patients were eradicated *H. pylori*.

Dual antimicrobial therapy (A+C)

Of the 24 patients with pretreatment isolates with clarithromycin resistance, 2 patients were eradicated of *H. pylori*.

Dual therapy (O+C)

Of the 4 patients with pretreatment isolates with clarithromycin resistance, no patients were eradicated *H. pylori*.

The data suggest that the use of the triple therapy regimen may overcome pretreatment clarithromycin resistance in a small number of patients. However, the majority of patients with pretreatment clarithromycin resistance failed the triple therapy regimen. Therefore, patients with clarithromycin resistant H. pylori should not be treated with any of the following: omeprazole/clarithromycin dual therapy, omeprazole/clarithromycin/amoxicillin triple therapy, or other regimens which include clarithromycin as the sole antimicrobial agent.

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Amoxicillin

The total population in all three studies was tested against amoxicillin via the Etest methodology. These amoxicillin MICs and clinical/bacteriological outcomes are listed in Table 6.

Table 6.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes for All Patients in All Studies ^a

Amoxicillin Pretreatment Results	Amoxicillin Post-treatment Results		
	<i>H. pylori</i> negative - eradicated	<i>H. pylori</i> positive - not eradicated Post-treatment susceptibility results <i>S</i> ^b MICs > 0.25 µg/mL No MIC	
Omeprazole + Clarithromycin + Amoxicillin			
Susceptible ^b 185	157	17 (11 C ^R) ^c	11
MICs > 0.25 ^b			
Clarithromycin + Amoxicillin			
Susceptible ^b 208	75	113	20
MICs > 0.25 ^b 3		1	2

^a Includes only patients with pretreatment amoxicillin susceptibility test results

^b Susceptible (S) MIC ≤ 0.25 µg/mL

^c Clarithromycin resistant

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CONCLUSION:

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Emerging Clarithromycin Resistance

Triple therapy (O+A+C)

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If the clarithromycin intermediate MICs are considered to be resistant the overall emerging resistance rate was 11 % (18/164) (only patients with post-treatment MICs) or 21.1 % (39/185) (considering patients who failed and did not have post-treatment MICs to be resistant). Of the patients who failed triple therapy, the emerging resistance rate was 19.8 % (18/91) (only patients with post-treatment MICs) or 34.8 % (39/112) (including patients without post-treatment MICs).

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LABELING

RECOMMENDATIONS:

The application is approvable. The package insert should reflect the susceptibility testing results obtained in the clinical studies as delineated in this review.

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/S/

Linda J. Utrup, Ph.D.
Expert Microbiology Review Officer

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CC:

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